**CONSENSUS DOCUMENT**

**Recommendations for the pharmacological treatment of hyperglycemia in type 2 diabetes**

Recomendaciones para el tratamiento farmacológico de la hiperglucemia en la diabetes tipo 2

Edelmiro Menéndez Torre*, Francisco Javier Lafita Tejedor†, Sara Artola Menéndez‡, Jesús Millán Núñez-Cortés§, Ángeles Alonso García¶, Manuel Puig Domingo**, José Ramón García Solans**, Fernando Álvarez Guisasola†, Javier García Alegría†, Javier Mediavilla Bravo‡, Carlos Miranda Fernández-Santos*, Ramón Romero González**

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*On behalf of the Working Group for Consensus and Clinical Guidelines of the Sociedad Española de Diabetes, Spain
†Sociedad Española de Arteriosclerosis (SEA), Spain
‡Sociedad Española de Cardiología (SEC), Spain
§Sociedad Española de Endocrinología y Nutrición (SEEN), Spain
¶Sociedad Española de Farmacología Comunitaria (SEFAC), Spain
†Sociedad Española de Medicina Familiar y Comunitaria (SEMFYC), Spain
‡Sociedad Española de Medicina Interna (SEMI), Spain
§Sociedad Española de Médicos de Atención Primaria (SEMERGEN), Spain
†Sociedad Española de Médicos Generales y de Familia (SEMG), Spain
‡Sociedad Española de Nefrología (SEN), Spain

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**Introduction**

Type 2 diabetes is a condition characterized by chronic hyperglycemia secondary to a dual pathogenetic mechanism: resistance to insulin action associated with progressive failure in pancreatic insulin secretion. Insulin resistance usually continues throughout the course of the disease, but may be improved with lifestyle changes (nutritional therapy and exercise), the achievement of more favorable anthropometric characteristics, and some drugs. Progressive failure in pancreatic insulin secretion should lead to early and active action being taken, with a gradual increase in...
both the dosage and number of drugs to maintain control objectives.

Some scientific societies\textsuperscript{1-6} have prepared consensus documents with recommendations regarding control objectives, stepped use of the different drugs, and the adaptation of both to the patient's characteristics. Such documents show both similarities and discrepancies because of the difficulties resulting from the lack of randomized, adequately powered clinical trials directly comparing the different treatment schemes recommended. The Board of the Spanish Society of Diabetes (SED) thus decided to commission our Working Group to prepare a document in which the available evidence and the different recommendations were adapted to the situation in Spain, taking into account that the final therapeutic decision will always depend on the physician, who must consider the specific characteristics of each patient. The Working Group considered that this document should be dynamic and regularly updated to take account of incoming evidence and on suggestions from SED members.

Control objectives

The achievement of good metabolic control may prevent or delay the occurrence of microvascular and macrovascular complications, as has been shown by various studies with long-term follow-up times in patients with both type 1 (DCCT/EDIC)\textsuperscript{7} and type 2 diabetes (United Kingdom Prospective Diabetes Study [UKPDS])\textsuperscript{8}. By contrast, if strict glycemic control is performed in patients with long-standing diabetes, advanced complications, or severe associated diseases, not only is there a greater cardiovascular prevention not achieved (Action in Diabetes and Vascular disease: preterAx DiamicroN MR Controlled Evaluation [ADVANCE])\textsuperscript{9} and Veterans Affairs Diabetes Trial [VADT])\textsuperscript{10}, but mortality may even increase (Action to Control Cardiovascular Risk in Diabetes [ACCORD])\textsuperscript{11}. Very strict control is therefore recommended in the early phases of diabetes treatment (glycosylated hemoglobin [HbA\textsubscript{1c}] < 6.5%), provided that the patient is not older than 70 years and has no advanced microvascular or macrovascular complications at the time of diagnosis or any associated diseases that make it advisable to avoid hypoglycemia. In this case, the recommended control HbA\textsubscript{1c} value would be < 7.5% or the best possible that would ensure treatment safety, adapted to the patient's condition and compatibility with concurrent drugs. It is generally admitted that approximately 10 years after disease onset, monotherapy is usually inadequate, and most patients will require combined treatment, often with insulin. When this occurs, it may be advisable to increase the control goal to HbA\textsubscript{1c} < 7.5% unless the traditional 7% goal is feasible and safe.

It should be borne in mind that hyperglycemia is only one of the cardiovascular risk factors in diabetic patients and that there are other associated risk factors such as dyslipidemia, hypertension, obesity, and smoking. These will greatly condition the potential occurrence of complications and patient survival. Thus, although it is beyond the scope of this document, the monitoring of these risk factors is expressly recommended as it has been shown to be highly effective (STENO-2)\textsuperscript{12}.

Therapeutic inertia

After treatment has been started, or if it has been changed, a number of aspects, such as metabolic control, should be assessed by measuring HbA\textsubscript{1c}, and evaluating capillary blood glucose profiles (when appropriate), tolerability of changes made, and the course of associated complications and diseases.

This must be done approximately every 3 months following the acute phase of treatment adjustment, and at least until the condition stabilizes. Then, when goals have been achieved, all patients must be monitored at least twice every year. If the changes made have not been effective in achieving the control objective in the initial 3 months and such failure has not been due to intercurrent diseases or use of drugs, treatment should be intensified and decision taking should not be delayed. It is extremely important to maintain good metabolic control, particularly in patients with recent onset of the disease, who may be asymptomatic despite failure to achieve the control objectives. The main barriers to treatment intensification may occur when a change in treatment requires an additional diabetological education process, as may occur for instance when secretagogues or insulin are started. These situations should be anticipated so as to avoid unnecessary delay.

It is important to plan medical and nursing action guidelines and drug treatment monitoring by the pharmacist for dose intensification, but it is equally important to plan the changes in treatment required by acute intercurrent conditions that may cause some degree of dehydration or difficult intake (febrile syndrome, vomiting, diarrhea, and so on). These conditions may make the current treatment of the patient unsafe and require its urgent modification\textsuperscript{13}.

Stepwise treatment

A number of drugs are currently available for the treatment of diabetes, including metformin, sulfonylureas, glinides, thiazolidinediones, disaccharidase inhibitors, dipeptidyl-peptidase 4 (DPP-4) inhibitors, and glucagon-like peptide-1 (GLP-1) receptor agonists, which, together with insulin, may be used as monotherapy or in combination. These drugs should be used after consideration of their respective prescribing information; some combinations have been shown to be safe, others are not recommended, and for still others long-term safety is unknown. The choice of treatment will depend on its potency to decrease HbA\textsubscript{1c}, the risk of inducing hypoglycemia and the degree of prior control, its influence on body weight and dyslipidemia, its preferential impact on basal or post-prandial blood glucose, any associated complications or diseases of the patient, the risk of drug-related adverse effects, tolerability, and cost (Table 1).

Initial drug treatment will vary depending on the prior degree of control, age, the presence of concurrent diseases, and the concomitant use of other drugs. As shown in the algorithm (Fig. 1), treatment will usually start with a single
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<tr>
<th>Table 1</th>
<th>Main characteristics of oral antidiabetic drugs</th>
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<td>Risk of hypoglycemia</td>
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<td>Metformin</td>
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<tr>
<td>Sulfonylureas</td>
<td>Glibenclamide (significant)</td>
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<td>Gliclazide (moderate/minimum)</td>
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<td>Glimepiride (moderate)</td>
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<td>Repaglinide (moderate)</td>
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<td>Nateglinide (minimum)</td>
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<td>Glinides</td>
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<td>DPP-4 inhibitors</td>
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<td>GLP-1 agonists</td>
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CHs, carbohydrates; GFR, glomerular filtration rate; GI, gastrointestinal.
Recommendations for the pharmacological treatment of hyperglycemia in type 2 diabetes

Drug, and two-drug treatment will be considered as a second step. Insulin or triple therapy may finally be required if the degree of control in the patient makes it advisable.

First step

Patients with HbA1c values ranging from 6.5% to 8.5%

The control goal (HbA1c < 6.5%) may be achieved in some patients with some lifestyle changes14, but this approach is not always effective because it depends on the patient’s characteristics and how well the patient follows the recommendations made. The SED thus recommends concomitant administration of metformin from the start in most patients15,16. In any case, the introduction of metformin should not be delayed for longer than 3 months if the control goal has not been achieved. To improve metformin tolerability, gradual dose titration is advised17. For example, half an 850-1,000 mg tablet may initially be given, which is increased to half a tablet every 12 h at 4-5 days if tolerability is good, and so on until a dose of 850-1,000 mg every 12 h is reached. If intolerance occurs, the drug should be reduced to the prior dose tolerated and dose increase should be attempted again with a longer time interval.

Alternatives to treatment with metformin if this is contraindicated or not tolerated include:

- First alternative: sulfonylureas. With a control goal of HbA1c < 6.5%, as potent secretagogues they involve a significant risk of hypoglycemia, but the risk is different depending on the active ingredient used18-20. A very careful dose titration and the preferential use of sustained release gliclazide or glimepiride should be considered. The use of glibenclamide or chlorpropamide is not recommended. Some studies suggest that sulfonylureas induce secondary beta cell failure sooner than metformin or glitazones21. They are also associated with a 1-3 kg weight increase22,23. Some guidelines do not recommend them in this treatment step.

- Second alternative: DPP-4 (dipeptidylpeptidase-4) inhibitors. These have clear advantages for use in this treatment step as an alternative to metformin if this is not tolerated. They involve a minimum risk of hypoglycemia when given as monotherapy and have no impact on patient weight24,25. Today, the main limitations on their use are the lack of studies showing their long-term efficacy and safety, and their high price. To date, only sitagliptin26 has been approved for this indication, although other active ingredients of the same class are pending authorization27,28.

- Third alternative: glinides. The option in this step is repaglinide30. Nateglinide should be used in combination because of its pharmacodynamic characteristics and potency36. In principle, it has the same limitations as sulfonylureas, but because of its characteristics and form of administration it may be suitable for patients with irregularities in diet and physical activity31,32.

- Fourth alternative: thiazolidinediones or glitazones. These require 10 to 12 weeks for maximum efficacy, and have a potency in terms of HbA1c reduction similar to...
metformin and sulfonylureas. Their potential side effects include weight increase, edema, anemia, fractures, and heart failure in some patient groups \cite{33,35}, which have limited their indication. In addition, it has not been clearly elucidated whether differences exist between rosiglitazone and pioglitazone, as has been suggested by some observational studies \cite{28}, and the question thus remains open until studies directly comparing both molecules are completed. These drugs may have a more relevant role in patients with severe metabolic syndrome \cite{37} and/or non-alcoholic steatohepatitis \cite{38}.

- **Fifth alternative: disaccharidase inhibitors.** These are less potent than the drugs mentioned above and are not associated with hypoglycemia when given as monotherapy. Their greatest limitation is intestinal intolerance, which requires treatment discontinuation in a high proportion of patients \cite{39}. Their greatest benefit is that they appear to significantly improve cardiovascular risk (STOP-NIDDM) \cite{40}. Two preparations have been marketed, acarbose and miglitol.

- **Sixth alternative: basal insulin.** In this step, insulin is reserved for patients in whom oral drugs are contraindicated.

### Initial treatment for patients with HbA1c > 8.5%

In patients with significant clinical signs of hyperglycemia (cardinal clinical signs and/or weight loss) at disease onset, treatment with insulin \cite{41-43}, alone or combined with metformin, is usually required. After initial control and improvements in glucotoxicity and lipotoxicity, insulin requirements are likely to gradually decrease, and control may be maintained in some cases with oral drugs, either as monotherapy or in combination.

In asymptomatic patients, it is advisable to start with metformin using a faster titration and, depending on response, to add a second drug \cite{44}, with monitoring of its course in the short term in order to adjust final treatment.

### Second step

In patients in whom control goals have not been achieved or who, after a period of adequate control, experience impairment due to the course of their diabetes (in the absence of any associated disease or drug increasing glyemia), a second drug should be added.

Long-term comparative studies are lacking for most drug combinations, which makes taking decisions difficult. In principle, it is recommended that associated drugs have different and complementary action mechanisms. Based on the response, dosage should be increased to the maximum effective dose, somewhat lower than the maximum dose allowed. It should also be borne in mind that the contraindications, limitations for use, and potential side effects are the same as those of both drugs separately.

### Combinations with metformin

- **Sulfonylureas and glinides.** Metformin-sulfonylurea combinations are the most widely tested and have been shown to be effective and safe \cite{42-45}, although doubt still exists about the increased mortality in a subgroup of patients seen in the UKPDS \cite{46} who started treatment with sulfonylureas and had metformin added in a second step. Various observational studies have addressed this issue \cite{47,51} and reported somewhat conflicting results, which moreover may not be superimposable on those obtained with more recent preparations. The risks for the control goal (HbA1c < 6.5%) are similar to those seen in monotherapy, and the same recommendations are therefore made. Glinides represents a viable alternative to sulfonylureas for patients with more irregular intake because of their short action period, and also for patients allergic to sulfonylides or, in the case of repaglinide, for patients with moderate renal failure \cite{52}. As regards the risk of hypoglycemia and weight increase, they may be considered as superimposable, with a potency lower than nateglinide \cite{53} and quite similar to repaglinide \cite{54}.

- **DPP-4 inhibitors.** These drugs, together with GLP-1 receptor agonists, form a novel group of secretagogues acting on both insulin and glucagon secretion. They have obvious advantages over sulfonylureas and glinides, including a low risk of hypoglycemia and weight neutrality \cite{55} and \cite{56}. However, their long-term safety and their impact on the course of diabetes and its complications are unknown. Their potency does not appear to be lower than that of sulfonylureas in terms of HbA1c reduction \cite{57,58}. They could be a preferential option in patients in whom hypoglycemia is unacceptable.

- **GLP-1 receptor agonists.** These are parenteral preparations achieving a stronger and longer effect on GLP-1 receptors than DPP-4 inhibitors. In the short-term studies published, they have been shown to improve glycemic control, especially post-prandial blood glucose, and partly also basal blood glucose \cite{59}. They slow gastric emptying, creating a sensation of satiety, which results in a sustained weight reduction in a substantial proportion of patients \cite{60,61}. They also achieve improvements in some vascular risk factors \cite{62}. In Spain, exenatide has been marketed for parenteral administration twice daily (before main meals, with an interval of at least 6 h between them) associated with metformin and/or sulfonylureas and with metformin plus glitazone \cite{63}, in patients with a body mass index greater than 30 kg/m². The marketing of liraglutide is pending at the time of writing these guidelines \cite{64}. We therefore recommend reading its prescribing information to assess its indications and limitations for use. This may be a highly useful drug class in patients in whom obesity is an essential problem, but its role as compared to other drugs or treatment approaches, such as surgery, has still to be defined.

- **Thiazolidinediones.** These drugs act by increasing insulin sensitivity by a different mechanism as compared to metformin, and are therefore frequently used in combination \cite{65-68}. In principle, they should mainly be indicated for patients with good post-prandial glucose control and elevated basal blood glucose not totally corrected with metformin. Their side effects are similar to those of each drug alone, and the same limitations as in monotherapy therefore apply.

- **Basal insulin.** The combination of basal insulin with metformin is a good therapeutic option of proven safety and efficacy \cite{69,70}. It is mainly indicated for patients with
good post-prandial control but with HbA1c above the
recommended objective. Although this approach increases
the rate of hyperglycemia, this is still much lower than
that found in patients with multiple insulin doses. It is a
good alternative for patients with in whom treatment
with glitazones is not appropriate.

• Disaccharidase inhibitors. Their combination with
metformin is safe, as no hypoglycemia will occur, but they
have a limited efficacy, with HbA1c decreases hardly
exceeding 0.5%79. Their main limitation is gastrointestinal
intolerance. They are therefore not recommended as an
alternative to a second drug in this therapeutic step.

Third step
In patients treated with two drugs with poor metabolic
control, the next step is insulin therapy. Except in patients
resistant to insulin therapy, there are no «advantages» in
delaying insulin introduction in the treatment regimen after
dual combined therapy has failed. The long-term benefit
and safety of an oral triple therapy as compared to insulin
use is uncertain because follow-up in the different clinical
trials is not longer than 12 months.

Combinations including no insulin
Among the different and valid combinations of oral agents,
the combination of metformin, sulfonylurea, and glitazone
is the most widely tested and most commonly used in clinical
practice. It would thus be the one recommended in most
patients with type 2 diabetes and poor control with dual
therapy73-77. In elderly patients78, the combination of
metformin, repaglinide, and glitazone may be safer. In
patients with limitations on the use of glitazones, the most
reasonable alternatives would be metformin plus
sulfonylureas plus DPP-4i79 or metformin plus repaglinide
plus DPP4i80, although these have the disadvantage that
they have been less widely tested.

Combinations including insulin
Most patients will have been treated with combinations of
metformin and secretagogues. To these, basal insulin is
added. If time since diabetes onset is longer than 10 years
and/or complications or intercurrent diseases have
occurred, the control goal will be revised to less than 7.5%
or the best possible that is considered safe for the patient.
This scheme may achieve a period of good control, but not
an excessively long one, to judge from the results of the 4T
study (Treating-To-Target in Type 2 diabetes)81. Hence, most
patients will require an intensified insulin regimen within
approximately 3 years. If this occurs, it is advisable to
continue treatment with metformin combined with insulin,
and to discontinue all other oral antidiabetic treatment.

Fourth step
As regards the possibility of quadruple therapy, which is a
feasible approach (due to the different pathophysiological
pathways from the pharmacological viewpoint), we think
that this is currently an investigational approach, rather
than a possibility in clinical practice.

Conclusions
Once lifestyle changes have been implemented, the goal
of drug treatment for type 2 diabetes will be to achieve an
optimized degree of metabolic control with the maximum
possible safety. The goal should be an HbA1c value < 6.5% in
the early stages of disease and < 7.5% in more advanced
stages or when there is a risk of hypoglycemia.

Treatment is divided into 3 steps. In the first step, and if
hyperglycemia is not too high (HbA1c, 6.5%-8.5%), metformin
is the drug of choice. Other alternative drugs will only be
used if metformin is not tolerated or is contraindicated. If
hyperglycemia is high (HbA1c > 8.5%), initial treatment
should consist of several oral drugs combined, or insulin
therapy should be started. The second step consists of the
addition of a second drug with a synergistic action. Various
options are available for this, and should be
individualized, based on the characteristics of each patient.
Finally, the third step implies the introduction of basal
insulin as a preferred option to oral triple therapy, which
must be reserved for insulin-resistant patients only.

Conflict of interest
The authors state that they have no conflict of interest.

Annex A.
Study promoted by the Spanish Society of Diabetes (SED) in
collaboration with:

Spanish Society of Atherosclerosis (SEA).
Spanish Society of Cardiology (SEC).
Spanish Society of Endocrinology and Nutrition (SEEN).
Spanish Society of Community Pharmacy (SEFAC).
Spanish Society of Family and Community Medicine
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Spanish Society of Internal Medicine (SEMI).
Spanish Society of Primary Care Physicians (SEMERGEN).
Spanish Society of General and Family Physicians (SEM).
Spanish Society of Nephrology (SEN).

Members of the Working Group for Consensus and Clinical
Guidelines of the Spanish Society of Diabetes:
Jose Juan Alemán Sánchez, Ramiro Antuña de Aláiz,
Francisco Javier Escalada San Martín, Fernando Escobar
Jiménez, Juan Carlos Ferrer García, José Antonio Fornos
Pérez, Ricardo García Mayor, Sonia Gaztambide Sáenz, María
Luisa López Fernández, José Luis Martín Manzano, Javier
Martínez Martín, Juan Carlos Méndez Segovia, Jorge Navarro
Pérez, Eduard Montanya Mías, Carlos Ortega Millán, Itxaso
Rica Etxebarría, and Teresa Tartón García.
Addendum to the Consensus Document «Recommendations for pharmacological treatment of hyperglycemia in type 2 diabetes»

As of September 23, 2010 the EMA decided to withdraw from the market all medicinal products containing rosiglitazone as an active ingredient (Avandia®, Avandamet® and Avaglim®) because the benefits of the drug were not considered to outweigh its potential risks. In this context, the FDA decided not to withdraw such products from the market, but proposed a number of pharmacovigilance measures. The FDA thinks that data suggesting a potential increase in cardiovascular risk associated with rosiglitazone are controversial and not definitive. Independent verification of the results of the RECORD study has been requested.

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Recommendations for the pharmacological treatment of hyperglycemia in type 2 diabetes

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